II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 35, 69, 74-77, 91-111, and 114-134 were pending in the case at the time of the Office Action. Claims 1-34, 36-68, 70-73, 78-90, and 112-113 have been canceled without prejudice or disclaimer. No claims have been amended, and no new claims have been added. Therefore, claims 35, 69, 74-77, 91-111, and 114-134 are currently under consideration.

B. The Claims Rejections Under 35 U.S.C. §112, First Paragraph, Are Overcome

Claims 69, 74-77, 91-111, and 114-134 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner argues that the newly claimed ranges of applicable molar ratios are not properly supported in the original disclosure. Applicants respectfully traverse.

The Federal Circuit has stated that the test for the written description requirement is "whether the application relied upon 'reasonably conveys to the artisan that the inventor had possession at the time of the later claimed subject matter.'" *In re Daniels*, 144 F.3d 1452, 1456, 46 USPQ2d 1788, 1790 (Fed. Cir. 1998). See also *Markman v. Westview Instruments, Inc.* 52 F.3d 967, 34 USPQ 2d 1321 (Fed. Cir. 1995) (en banc) ("Claims must be read in view of the specification, of which they are a part."). In rejecting a claim under the written description requirement of 35 U.S.C. §112, first paragraph, the Examiner has the initial burden of presenting evidence or reasons why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined in the claims. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). Accordingly, the Examiner is required: (1) to set forth the claim limitation not described; and (2) to provide reasons why a person skilled in the art would not have recognized the description of the limitation in view of the disclosure of the application

as filed. *Interim Guidelines for the Examination of Patent Applications Under 35 USC 112, Paragraph 1*, Chisum on Patents, vol. 3, §7.04[1][c].

Regarding the rejected claims, claim 69 and its dependent claims are directed to methods for disinfecting and/or sterilizing a floor, a table-top, a counter-top, hospital equipment, a wheel chair, gauze, cotton, silk, or a medical device comprising applying a composition that includes a particular combination of basic reagents and dyes, wherein the molar ratio of basic reagent:dye in the composition is 1:1 to 25:1. Claim 74 and its dependent claims are directed to methods for disinfecting and/or sterilizing a fluid that involving adding a composition comprising a specific basic reagent and dye, wherein the molar ratio of dye:basic reagent in the composition is 10:1 to 65:1. Claim 98 and its dependent claims are directed to methods for disinfecting and/or sterilizing a floor, a table-top, a counter-top, hospital equipment, a wheel chair, gauze, cotton, silk or a medical device comprising applying a composition that includes chlorhexidine and brilliant green to the surface, wherein the molar ratio of chlorhexidine:brilliant green in the composition is 1:1 to 25:1.

Support for the claims as written can be found generally throughout the specification, including the claims as originally filed. Regarding recited molar ratios in the claims, explicit support can be found on page 4, line 26 to page 5, line 6 of the specification. The phrase "[t]his includes all the intermediate ranges as well" makes it clear that ranges of the recited molar ratios are contemplated. Specification, page 4, line 31. Thus, the specification satisfies the written description requirement because it reasonably conveys to one of skill in the art that they had possession of the claimed subject matter. *In re Daniels*, 144 F.3d 1452, 1456, 46 U.S.P.Q.2d 1788, 1790.

Based on the foregoing, it is respectfully requested that the written description rejection be withdrawn.

C. The Rejections Under 35 U.S.C. §103(a) Are Overcome

1. Rejection of Claim 35 Based on Shlenker

Claim 35 is rejected under 35 U.S.C. §103(a) as being unpatentable over Shlenker *et al.* (U.S. Patent 5,965,276; "Shlenker"). The Examiner argues that Shlenker teaches an antiseptic compound that includes gentian violet bound to biocides such as chlorhexidine, and that it would have been obvious to one of ordinary skill in the art to combine gentian violet and chlorhexidine to achieve a compound that includes the two bound together. Applicants respectfully traverse.

The Examiner cites to col. 5, lines 5-15, col. 6, lines 10-18, and col. 16, lines 16-30 to support this rejection. Regarding col. 5, lines 5-15, this section does not provide any teaching or suggestion pertaining to binding of gentian violet to chlorhexidine. Rather, it pertains to a "thickened mixture" that is "applied over the latex layer," and that gentian violet can be "thickened with a mixture of polyethylene oxide and glycerin." There is no mention of chemical binding of one molecule to another in this section. Similarly, col. 6, lines 10-18 is also insufficient because it merely discloses a list of biocides for use in the membranes according to the disclosure, among which are mentioned gentian violet and chlorhexidine. Again, there is no teaching or suggestion in this section pertaining to binding of gentian violet to any basic reagent. Regarding the Examiner's citation of col. 16, lines 16-30, this section does not pertain to binding of gentian violet to a basic reagent, but rather pertains to a discussion regarding chemical bonding of polyurethane to certain biocide molecules. The disclosure in this section is specific for binding to polyurethanes. One of ordinary skill in the art would understand this to be the case since the specification indicates that "[p]olyurethanes possess the advantage that the urethane and urea linkages in the chains are relatively reactive." col. 16, lines 7-8. One of

ordinary skill in the art would not understand that this section teaches or suggests binding of gentian violet to a basic reagent such as chlorhexidine because chlorhexidine does not include "reactive urethane and urea linkages." col. 16, lines 7-8. Further, Schlenker actually teaches away from the claimed invention because it teaches that loss of biocidal activity is a problem that can be encountered when there is binding to a biocide molecule. See col. 16, lines 15-17.

Thus, there is no evidence that Schlenker would have prompted one of ordinary skill in the art to lead to the claimed antiseptic compounds. In fact, as set forth above, it actually teaches away from the claimed biocidal compounds.

In view of the foregoing, it is respectfully requested that the rejection of claim 35 under 35 U.S.C. §103(a) should be withdrawn.

2. Rejection of Claims 69, 74-77, 91-93, 95-96, 99-100, 103-107, 109-111, 114-119, 121-122, and 124-134 Based on Shlenker

Claims 69, 74-77, 91-93, 95-96, 99-100, 103-107, 109-111, 114-119, 121-122, and 124-134 are rejected under 35 U.S.C. §103(a) as being unpatentable of Shlenker. Shlenker is said to teach biocidal compounds for application to a plurality of surfaces, with preferred use of gentian violet in combination with another biocide, with chlorhexidine being preferred. While the Examiner concedes that Shlenker is silent as to applicable molar ratios of compound components, she argues that it would have required mere routine experimentation to determine applicable ratios of the known components taught in Shlenker. Applicants respectfully traverse.

a. The Examiner has Failed to Establish a *Prima facie* Case of Obviousness

There is no *prima facie* case of obviousness because the Examiner has not cited any teaching, suggestion, or motivation to one of ordinary skill in the art to provide for the claimed

range of basic reagent and dye. There are a potentially vast number of possible combinations of any basic reagent and any dye. Nothing in Schlenker provides any teaching or suggestion to provide for the specific combination of basic reagent and dye in the range of molar ratios set forth in the claims. Nor has the Examiner cited any teaching or suggestion to provide for the missing limitation. She merely argues that it is a matter of routine experimentation to provide for the range of ratios of dye:basic reagent.

According to *KSR International v. Teleflex Inc.*, 127 S. Ct. 1727, 1736 (U.S. 2007):

> To determine whether there was an apparent reason to combine the known elements in the way a patent claims, it will often be necessary to look at interrelated teachings of multiple patents; to the effects of demands known to the design community or present in the market place; and to the background knowledge possessed by a person having ordinary skill in the art. To facilitate review, this analysis ***should be made explicit***. (emphasis added).

Here there is no explicit analysis because nothing has been cited by the Examiner which provides any suggestion or motivation to one of ordinary skill in the art to choose the particular basic reagent and dye recited in the claims at a ratio that falls within the recite ranges in the claims.

Therefore, in the absence of a teaching or suggestion as to each limitation of the claimed invention, there can be no *prima facie* case of obviousness.

b. Applicants' Methods Are Synergistic Compared to Methods Using Dye Alone or Basic Reagent Alone

Even if the Examiner argues that a *prima facie* case of obviousness has been made, which Applicants as discussed above assert is not the case, Applicants would still overcome any obviousness rejection because Applicants' methods are surprisingly and unexpectedly superior compared to methods using either dye alone or basic reagent alone.

The Example section of the above-referenced patent application provides strong evidence of synergy of gentian violet (GV) and chlorhexidine (CHX) as an antiseptic/disinfectant. Table 2 and Table 3 on page 20 of the referenced patent application show zones of inhibition (ZOI) produced by coated endotracheal PVC tubes (using DCM or MeOh). As set forth in the application on page 20, lines 16-19, "endotracheal PVC tubes impregnated with Gendine (GN) are far more effective against all organisms when compared with those impregnated with CHX, and more effective than PVC tubes impregnated with GV against *Pseudomonas aeruginosa.*"

Table 4 on page 21 of the referenced application shows ZOI produced by coated silicone catheters. Page 21, lines 10-12 states that "data in Table 4 shows how silicone catheters impregnated with GN are more effective in inhibiting *MRSA, PS* and *C. parapsilosis* than catheters impregnated with either GV or CHX."

Table 5, on page 21 of the present application, shows ZOI produced by coated polyurethane catheters (PU). Page 21, lines 24-27 states that "PU catheters impregnated with GN are more effective than PU catheter impregnated with GV in inhibiting *Pseudomonas aeruginosa,* and more effective than PU catheters impregnated with CHX against all three organisms, *MRSA, PS* and *C. parapsilosis*."

Table 6, on page 22 of the present application, shows ZOI produced by coated silk sutures. Page 21, lines 10-12 provides that "silk sutures coated or impregnated with GN are significantly more effective in inhibiting MRSA, PS and *C. parapsilosis* than sutures coated with either GV or CHX."

Similarly, Tables 7-10 on pages 24-25 show similar synergy against various bacterial and fungal organisms, when GV was combined with other basic reagents on the surfaces of medical devices.

Furthermore, as set forth in the Declaration of one of the inventors, Dr. Issam Raad (filed with the response to the Office Action dated January 11, 2006), additional evidence was provided demonstrating that the combination of a basic reagent and a dye has antiseptic ability as a mouthwash, coating of a glove, or coating of a catheter than is more than additive compared to either dye alone or basic reagent alone.

In addition, the second Declaration of Dr. Issam Raad ("the Second Declaration; Exhibit A), filed with the response to the Office Action dated July 25, 2006, sets forth a summary of data from his laboratory that further demonstrates a high level of synergy of the combination of a basic reagent and a dye in antiseptic ability. Second Declaration, ¶8 and Exhibit 1 of Second Declaration.

Dr. Raad notes that the most serious forms of catheter related bloodstream infections are those caused by fungi, particularly *Candida albicans*. Second Declaration, ¶9. This is the infection with the highest mortality rate – around 40%. *Id.* His laboratory team found that gendine (GV and CHX) mixed in a specific molar ratio to coat catheters and devices provides unexpectedly superior synergy against *Candida albicans*. *Id.* The strain used in the studies summarized in Exhibit 1 was obtained from a patient who suffered from catheter-related fungemia/candidemia caused by *Candida albicans* (strain 009-3072). *Id.* In the first part of the study summarized in Exhibit 1, they calculated a minimal inhibitor concentration (MIC) and minimal fungicidal concentration (MBC) for each of the components, GV and CHX. The MIC/MBC was 0.5 microgram per mL for the GV and 16 microgram per mL for CHX. *Id.*

Dr. Raad's group then tested for synergy of the combination of CHX and GV over a range of 1:1 to 100:1, and obtained the results described on page 2 of Exhibit 1. Second Declaration, ¶10. Boxes that are shaded had a complete kill of the *Candida albicans* at the

respective concentrations of the components that are lower that the MIC and MBC of CHX alone and GV alone. *Id.* The best synergistic data was obtained at a ratio of CHX:GV of 1:1 and 10:1, with a plateauing effect at 25:1 and thereafter. *Id.* In other words, Dr. Raad's team found that there is synergy obtained at 50:1 and 100:1 but it is not appreciably different from 25:1. *Id.*

As noted by Dr. Raad, these results clearly establish that the claimed methods using a combination of a dye and basic reagent are surprisingly and unexpectedly superior compared to methods of disinfecting using dye alone or basic reagent alone. Second Declaration, ¶11.

Further, Dr. Raad's group has published a study (Bahna *et al.*, Oral Oncol. 2007 Feb.; 43(2):159-64; Exhibit 2) that demonstrates that mouthwash compositions that have a ratio of dye:basic reagent of 10:1-66:1 demonstrated synergistic antimicrobial efficacy against free-floating and biofilm forms of *Candida albicans*. Second Declaration, ¶12.

The Examiner argues in the Office Action that the data in the specification and the information set forth in the Declarations of Dr. Raad are insufficient to demonstrate a synergistic effect of the claimed methods. In response to this assertion, Applicants herein submit the Declaration of Ray Hachem, (Exhibit B, hereinafter the "Hachem Declaration). Dr. Hachem is a skilled expert in infectious disease therapy and control. Hachem Declaration, ¶3. His expertise is set forth in ¶3 of his declaration. A copy of his curriculum vitae is attached is Appendix A. Dr. Hachem was asked whether the results set forth in the present patent application and the information set forth in the first and second Declarations of Dr. Raad demonstrate that the presently claimed invention demonstrates a synergistic antiseptic effect compared to dye alone or basic reagent alone. Hachem Declaration, ¶5. Dr. Hachem has cited to a definition of "synergy" from the 2007 instructions to authors from the journal entitled "Antimicrobial Agents and Chemotherapy." Hachem Declaration, ¶6. In paragraph 6 of his declaration, Dr. Hachem cites

to specific sections of the patent application and evidence from the declarations of Dr. Raad which demonstrate synergy. He concludes that the results set forth in the specification and the data cited in the Raad declarations clearly establishes that compositions that include a dye and basic reagent in the molar ratios set forth in the claims exhibit surprising and unexpected synergy for disinfecting and/or sterilizing surfaces or a fluid compared to dye alone or basic reagent alone. Hachem Declaration, ¶8.

Thus, to the extent that the Examiner might have set forth any *prima facie* case of obviousness, it has been successfully rebutted.

3. Rejection of Claim 94 Based on Shlenker and Further in View of Dangman

Claim 94 is rejected under 35 U.S.C. §103(a) as being unpatentable over Shlenker as applied above, and further in view of Dangman. Claim 94 recites "wherein the surface [to be disinfected and/or sterilized] is a silk suture." The Examiner argues that it would have been obvious to one of ordinary skill in the art to apply the compound of Shlenker to the conventional glove construction taught by Dangman, which she asserts includes silk fibers, because the common goal in both references is to provide antibacterial protection to both gloved workers and patients. Applicants respectfully traverse.

Applicants note that neither Dangman nor Shlenker provide any information pertaining to sutures. The Examiner has not set forth how one of ordinary skill in the art would be motivated to coat a silk suture with the claimed composition based on the teaching of either reference. The references pertain to gloves, and not sutures.

Further, for the reasons discussed above, the discussion of which is herein incorporated into this section, there is additionally not *prima facie* case of obviousness for the reasons discussed above based on Shlenker. As discussed above, Shlenker does not provide any

teaching, suggestion, motivation, or other information to provide for the claimed molar ratios of dyes and basic reagents as set forth in the claims. Nor does Dangman remedy the deficiencies of Shlenker because it is only cited for teaching silk fibers as a glove material.

Further, as summarized in paragraph 5 of the second Declaration of Dr. Raad, the instant specification demonstrates that silk sutures coated or impregnated with Gendine are significantly more effective in inhibiting MRSA, PS, and *C. parapsilosis* than sutures coated with either Gentian violet or chlorhexidine.

In view of the foregoing, it is respectfully requested that the rejection of claim 94 under 35 U.S.C. §103(a) based on Shlenker in view of Dangman should be withdrawn.

4. Rejection of Claims 97, 101-102, 108, 120, and 123 Based on Shlenker and Further in View of Williford or Dow

Claims 97, 101-102, 108, 120, and 123 are rejected under 35 U.S.C. §103(a) as being unpatentable over Shlenker as applied above and further in view of either Williford (U.S. Patent No. 5,261,169) or Dow (U.S. Patent 5,120,325). The Examiner cites to Williford and Dow as teaching that gentian violet and brilliant green are functionally equivalent dyes in applications directed to body and organic surface contact, and that it would have been obvious to one of ordinary skill in the art to substitute brilliant green for the gentian violet taught in Shlenker because of their recognized functional equivalence. Applicants respectfully traverse.

Williford is a U.S. Patent pertaining to a system and method for deodorant delivery in footwear. Williford makes a single reference to brilliant green gentian violet as examples of a dye. Col. 10, lines 20-21. Contrary to the Examiner's assertion, it fails to provide any indication that gentian violet and brilliant green are ***functionally equivalent*** as dyes or as antiseptics. The section of Williford where these dyes are discussed is in a section which concerns substances

which may be incorporated into polymeric bead delivery systems for footwear. Williford does not appear to concern gloves, nor does the discussion pertaining to brilliant green concern formation of a membrane as discussed in Shlenker.

Dow concerns color-matched sterile adhesive bandages containing melanin-like pigment compositions. See abstract. Dow lists gentian violet and brilliant green among a long list of agents which can be incorporated into its bandages. Col. 4, line 30 – col. 5, line 26. While it lists these two agents as dyes, it ***does not provide any indication that these dyes are functionally equivalent as dyes or as antiseptics***. One of ordinary skill in the art would understand that these agents have different chemical properties, and would thus not be considered to be functionally equivalent. A MedLine search of the medical literature using PubMed did not reveal any study showing that melanin dyes are associated with an antimicrobial activity.

Further, for the reasons discussed above, the discussion of which is herein incorporated into this section, there is additionally not *prima facie* case of obviousness for the reasons discussed above based on Shlenker. As discussed above, Shlenker does not provide any teaching, suggestion, or motivation to provide for the claimed molar ratios of dyes and basic reagents as set forth in the claims. Nor does Williford or Dow remedy the deficiencies of Shlenker because these references are cited only as teaching brilliant green.

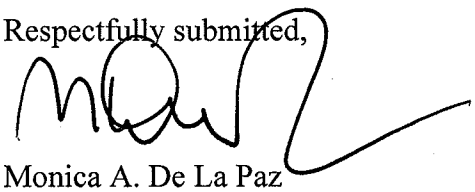
In view of the foregoing, it is respectfully requested that the rejection of claims 97, 101-102, 108, 120, and 123 under 35 U.S.C. §103(a) based on Shlenker in view of Williford or Dow should be withdrawn.

D. Conclusion

In view of the foregoing, it is respectfully submitted that each of the pending claims is in condition for allowance, and a Notice of Allowance is earnestly solicited. The Examiner is

invited to contact the undersigned attorney at (512) 536-5639 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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